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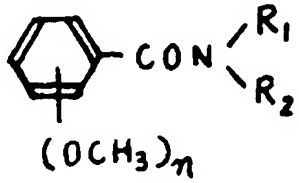
(54) BLOOD SUGAR LEVEL DEPRESSING AGENT

(57) Abstract:

PURPOSE: To provide a blood sugar level depressing agent containing a compound such as 4-methoxy-N-3-pyridylbenzamide, etc. as an active component, and having excellent blood sugar level depressing effect and long duration of the activity.

CONSTITUTION: The agent contains the compound of formula[R_1 is H or lower alkyl; R_2 is straight-chain, branched-chain or cyclic alkyl, (nuclear-substituted) pyridyl, or pyridylmethyl; n is 1W3]as an active component. The active compound of formula can be prepared easily by reacting an amine with a methoxybenzoyl chloride in the presence of a base such as triethylamine by conventional process. It is administered in an arbitrary form prepared by the conventional means for the preparation of ordinary drug preparation.



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⑬公開　昭和58年(1983)4月26日
発明の数　1
審査請求　未請求
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⑤4血糖降下剤

⑳特　　願　昭56—167934
㉒出　　願　昭56(1981)10月22日
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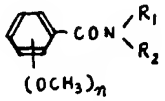
明　細　書

1. 発明の名称

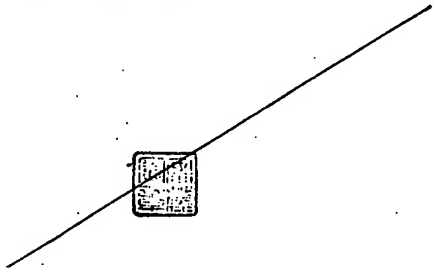
血糖降下剤

2. 特許請求の範囲

一般式

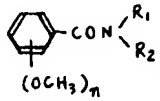


(式中、R_1は水素原子又は低級アルキル基を示し、R_2は直鎖，分岐鎖又は環式アルキル基、核に置換基を有し得るピリジル基又はピリジルメチル基を示し、nは1～3を示す。)で表わされる化合物を有効成分とする血糖降下剤。



3. 発明の詳細な説明

本発明は、次の一般式

 　〔I〕

(式中、R_1は水素原子又は低級アルキル基を示し、R_2は直鎖，分岐鎖又は環式アルキル基、核に置換基を有し得るピリジル基又はピリジルメチル基を示し、nは1～3を示す。)で表わされる化合物を有効成分とする血糖降下剤の発明である。

上式〔I〕で表わされる化合物の中には、公知の化合物が含まれるが、それらの記載されている先行文献には血糖降下作用ないしそれを示唆する薬理作用は全く記載されていない。

上式〔I〕で表わされる本発明の化合物は、例えば、以下の参考例に示すように、アミン類とメトキシベンゾイルクロライド類とを、塩基、例えばトリエチルアミンの存在下常法により反応させることにより容易に得ることができる。

参考例.

3-アミノピリジン9.4g，トリエチルアミン15mℓ及びアセトン200mℓの混合溶液に、氷冷撹拌下、4-メトキシベンゾイルクロライド17gを徐々に加える。同温度で30分、次いで室温で1時間撹拌後反応溶液を1ℓの水に注ぎ、析出する結晶を戸取し、水洗後メタノールから再結晶して無色針状晶の4-メトキシ-N-3-ピリジルベンズアミド(化合物1)17.5gを得た。収率77%，融点168～170℃

元素分析値　分子式 $C_{13}H_{12}N_2O_2$ として

	C	H	N
理論値(%)	68.41	5.30	12.27
実測値(%)	68.33	5.27	12.24

上記と同様にして表1の化合物を得た。

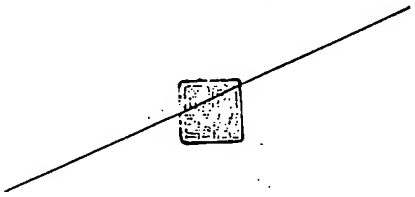
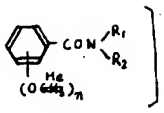


表1



No.	-(OMe)n	R_1	R_2	分子式	融点(℃)	収率(%)	元素分析値 理論値(%) 実測値(%)	C	H	N
2	2-OMe	H		$C_{13}H_{12}N_2O_2$	112～114	76		68.41 68.49	5.30 5.24	12.27 12.31
3	〃	〃		$C_{14}H_{14}N_2O_2$	80～82	83		69.40 69.32	5.83 5.80	11.56 11.59
4	〃	〃		$C_{15}H_{16}N_2O_2$	85～87	91		70.29 70.24	6.29 6.23	10.93 10.99
5	3-OMe	〃		$C_{13}H_{12}N_2O_2$	121～122	85		68.41 68.48	5.30 5.36	12.27 12.21
6	〃	〃		〃	155～156	83		68.41 68.43	5.30 5.31	12.27 12.30
7	〃	〃		$C_{14}H_{14}N_2O_2$	99～101	88		69.40 69.47	5.83 5.79	11.56 11.60
8	4-OMe	〃		$C_{13}H_{12}N_2O_2$	131～132	79		68.41 68.35	5.30 5.26	12.27 12.31
9	〃	〃		$C_{14}H_{14}N_2O_2$	150～153	65		69.40 69.36	5.83 5.79	11.56 11.52
10	〃	〃		〃	71～73	68		69.40 69.47	5.83 5.78	11.56 11.58
11	〃	〃		〃	61～64	77		69.40 69.45	5.83 5.88	11.56 11.63
12	〃	〃		$C_{15}H_{16}N_2O_2$	136～137	82		70.29 70.37	6.29 6.34	10.93 10.89

13	2,3-(OMe)$_2$	H		$C_{14}H_{14}N_2O_3$	117~118	58	65.10 65.14	5.46 5.49	10.85 10.91
14	〃	〃		$C_{15}H_{16}N_2O_3$	110~111	62	66.16 66.12	5.92 5.95	10.29 10.33
15	〃	〃		$C_{16}H_{18}N_2O_3$	111~112	67	67.11 67.14	6.34 6.37	9.78 9.75
16	2,4-(OMe)$_2$	〃		$C_{15}H_{16}N_2O_3$	98~99	51	66.16 66.11	5.92 5.87	10.29 10.34
17	〃	〃		〃	140~141	69	66.16 66.21	5.92 5.96	10.29 10.31
18	〃	〃		$C_{16}H_{18}N_2O_3$	93~94	63	67.11 67.15	6.34 6.39	9.78 9.74
19	2,6-(OMe)$_2$	〃		$C_{15}H_{16}N_2O_3$	155~156	67	66.16 66.22	5.92 5.97	10.29 10.24
20	〃	〃		$C_{16}H_{18}N_2O_3$	206~209	63	67.11 67.07	6.34 6.39	9.78 9.80
21	3,4-(OMe)$_2$	〃		$C_{14}H_{14}N_2O_3$	84~86	79	65.10 65.16	5.46 5.41	10.85 10.87
22	〃	〃		〃	49~51	88	65.10 65.08	5.46 5.43	10.85 10.88
23	〃	〃		$C_{15}H_{16}N_2O_3$	122~123	63	66.16 66.12	5.92 5.97	10.29 10.24
24	〃	〃		〃	128~129	74	66.16 66.19	5.92 5.88	10.29 10.33
25	〃	〃		〃	131~132	75	66.16 66.20	5.92 5.96	10.29 10.25

26	3,4-(OMe)$_2$	H		$C_{16}H_{18}N_2O_3$	69~71	63	67.11 67.15	6.34 6.37	9.78 9.77
27	〃	〃	i-Pr	$C_{12}H_{17}NO_3$	144~145	85	64.55 64.59	7.68 7.61	6.27 6.23
28	〃	〃	n-Bu	$C_{13}H_{19}NO_3$	83~84	88	65.80 65.78	8.07 8.03	5.90 5.84
29	〃	〃	s-Bu	〃	127~128	83	65.80 65.84	8.07 8.04	5.90 5.93
30	〃	〃	i-Bu	〃	124~125	80	65.80 65.85	8.07 8.11	5.90 5.95
31	〃	〃		$C_{15}H_{21}NO_3$	181~182	91	68.41 68.36	8.04 8.07	5.32 5.36
32	3,5-(OMe)$_2$	〃		$C_{15}H_{16}N_2O_3$	96~97	85	66.16 66.12	5.92 5.98	10.29 10.32
33	〃	〃		$C_{16}H_{18}N_2O_3$	119~120	87	67.11 67.18	6.34 6.37	9.78 9.72
34	3,4,5-(OMe)$_3$	〃		$C_{15}H_{16}N_2O_4$	154~156	65	62.49 62.53	5.59 5.64	9.72 9.71
35	〃	〃		〃	157~158	77	62.49 62.52	5.59 5.56	9.72 9.73
36	〃	〃		$C_{16}H_{18}N_2O_4$	115~116	58	63.56 63.52	6.00 6.04	9.27 9.25
37	〃	〃		〃	145~146	69	63.56 63.51	6.00 6.07	9.27 9.22
38	〃	〃		〃	127~128	64	63.56 63.59	6.00 6.03	9.27 9.29

39	3,4,5-(OMe)$_3$	H		$C_{17}H_{20}N_2O_4$	145～146	71	64.54 64.58	6.37 6.32	8.86 8.90
40	〃	〃	n-Pr	$C_{13}H_{19}NO_4$	114～115	73	61.64 61.60	7.56 7.59	5.53 5.57
41	〃	〃	i-Pr	〃	154～155	77	61.64 61.66	7.56 7.54	5.53 5.58
42	〃	〃	n-Bu	$C_{14}H_{21}NO_4$	133～134	80	62.90 62.87	7.92 7.86	5.24 5.27
43	〃	〃	s-Bu	〃	162～163	75	62.90 62.95	7.92 7.94	5.24 5.20
44	〃	〃	t-Bu	〃	133～134	79	62.90 62.91	7.92 7.88	5.24 5.29
45	〃	〃	i-Bu	〃	122～123	81	62.90 62.96	7.92 7.87	5.24 5.28
46	〃	〃		$C_{16}H_{23}NO_4$	182～183	88	65.51 65.54	7.90 7.93	4.78 4.72
47	〃	i-Pr	i-Pr	$C_{16}H_{25}NO_4$	127～128	72	65.06 65.11	8.53 8.59	4.74 4.71

このようにして得られる本発明の化合物は、優れた血糖降下作用を有し、ヒトに対しては0.1～100mg／kgで有効で、1日1回0.1～100mg／kgの投与で24時間以上その効力を持続する。

投与に際しては、通常の製剤化に用いられる慣用手段により所望の剤型に成形された製剤が用いられる。

実施例1.

1群5匹の5週令DDY系マウス（雄，体重25～30g）を16時間絶食後、アロキサン75mg／kgを静脈内に投与し、48時間後に、本発明化合物（200mg／kg）の水溶液又はけん濁液を経口投与し、150分後に心臓から採血し、グルコースオキシダーゼ法により血中糖値を測定した。測定結果を表2に例示する。

なお、表中の化合物番号は、後記例の化合物番号に対応している。

表 2

投与化合物	血糖値（mg/dl） mean ± S. D.
なし(対照)	$47^{3}_{}$ ± 28
1	326 ± 42**
3	378 ± 31**
4	364 ± 19***
6	378 ± 52*
7	412 ± 33*
12	383 ± 28**
17	345 ± 41***
22	378 ± 37**
25	355 ± 46**
26	336 ± 32***
27	407 ± 30*
28	402 ± 24**
29	421 ± 27*
32	416 ± 23*
33	402 ± 34*
36	416 ± 21**
38	307 ± 43***
39	412 ± 31*
41	421 ± 28*
46	383 ± 41**

*：P＜0.05，**：P＜0.01，***：P＜0.001

実施例2

4-メトキシ-N-3-ピリジルベンズアミド(化合物1)	100 部
リン酸水素カルシウム	58.5部
結晶セルロース	50 部
コーンスターチ	40 部
ステアリン酸カルシウム	1.5部

これらをよく混合し、常法により1錠250mgに打錠(有効成分100mg含有)し、血糖降下用錠剤として用いる。

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代理人　安藤憲章

第1頁の続き

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DRAFT TRANSLATION

from

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JAPANESE PATENT APPLICATION (A)

No. 58-069812

A HYPOGLYCEMIC AGENT

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Examination request: Not yet made

Number of Inventions: 1

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213/75		7138-4C

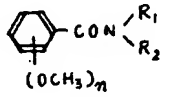
Specification

1. Title of Invention

Hypoglycaemic agent

2. Patent Claim

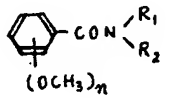
Hypoglycemic agent which has a compound represented by the following formula as the active component.



[In the formula, R_1 denotes hydrogen atom or lower alkyl group, R_2 denotes a linear, branched or cyclic alkyl group, a pyridyl group which may have a substituent on the nucleus or a pyridylmethyl group, and n denotes 1-3].

3. Detailed Description of the Invention

This invention is the invention of a hypoglycemic agent which has a compound represented by the following formula (I) as the active component



[I]

[In the formula, R_1 denotes hydrogen atom or lower alkyl group, R_2 denotes a linear, branched or cyclic alkyl group, a pyridyl group which may have a substituent on the nucleus or a pyridylmethyl group, and n denotes 1-3].

Known compounds are included in the aforesaid compound represented by the formula (I), but in the previous literature in which they are mentioned, there is no mention at all of a hypoglycemic effect or a pharmacological action suggesting this.

The compounds of this invention represented by the aforesaid formula (I) may be obtained readily by usual methods of reacting an amine compound with a methoxybenzoyl chloride compounds in the presence of a base such as triethylamine, as illustrated in the following reference example.

Reference Example

4-methoxybenzoyl chloride 17 g was added gradually under ice cooling and stirring to a mixed solution of 3-aminopyridine 9.4 g, triethylamine 15ml and acetone 200 ml. After stirring for 30 minutes at the same temperature then for 60 minutes at room temperature, the reaction solution was poured into 1 l of water, and the crystals which precipitated were collected by filtration and washed with water, then re-crystallised from methanol, to obtain 175 g of colourless acicular crystals of 4-methoxy-N-3-pyridylbenzamide (compound 1), melting point 168-170°C.

Elemental analysis	as molecular formula $C_{13}H_{12}N_2O_2$		
	C	H	N
theoretical value (%)	68.41	5.30	12.27
experimental value (%)	68.33	5.27	12.24

The compounds of Table 1 were obtained in the same way.

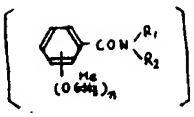


Table 1

No.	-(OMe)n	R_1	R_2	Molecular formula	Melting point (°C)	Yield (%)	Elemental anal. values Calc(%) C	H	N
							Found(%) C	H	N
2	2-OMe	H		$C_{13}H_{12}N_2O_2$	112~114	76	68.41	5.30	12.27
							68.49	5.24	12.31
3	〃	〃		$C_{14}H_{14}N_2O_2$	80~82	83	69.40	5.83	11.56
							69.32	5.80	11.59
4	〃	〃		$C_{15}H_{16}N_2O_2$	85~87	91	70.29	6.29	10.93
							70.24	6.23	10.99
5	3-OMe	〃		$C_{13}H_{12}N_2O_2$	121~122	85	68.41	5.30	12.27
							68.48	5.36	12.21
6	〃	〃		〃	155~156	83	68.41	5.30	12.27
							68.43	5.31	12.30
7	〃	〃		$C_{14}H_{14}N_2O_2$	99~101	88	69.40	5.83	11.56
							69.47	5.79	11.60
8	4-OMe	〃		$C_{13}H_{12}N_2O_2$	131~132	79	68.41	5.30	12.27
							68.35	5.26	12.31
9	〃	〃		$C_{14}H_{14}N_2O_2$	150~153	65	69.40	5.83	11.56
							69.36	5.79	11.52
10	〃	〃		〃	71~73	68	69.40	5.83	11.56
							69.47	5.78	11.58
11	〃	〃		〃	61~64	77	69.40	5.83	11.56
							69.45	5.88	11.63
12	〃	〃		$C_{15}H_{16}N_2O_2$	136~137	82	70.29	6.29	10.93
							70.37	6.34	10.89
13	2,3-$(OMe)_2$	H		$C_{14}H_{14}N_2O_3$	117~118	58	65.10	5.46	10.85
							65.14	5.49	10.91
14	〃	〃		$C_{15}H_{16}N_2O_3$	110~111	62	66.16	5.92	10.29
							66.12	5.95	10.33
15	〃	〃		$C_{16}H_{18}N_2O_3$	111~112	67	67.11	6.34	9.78
							67.14	6.37	9.75
16	2,4-$(OMe)_2$	〃		$C_{15}H_{16}N_2O_3$	98~99	51	66.16	5.92	10.29
							66.11	5.87	10.34
17	〃	〃		〃	140~141	69	66.16	5.92	10.29
							66.21	5.96	10.31
18	〃	〃		$C_{16}H_{18}N_2O_3$	93~94	63	67.11	6.34	9.78
							67.15	6.39	9.74
19	2,6-$(OMe)_2$	〃		$C_{15}H_{16}N_2O_3$	155~156	67	66.16	5.92	10.29
							66.22	5.97	10.24
20	〃	〃		$C_{16}H_{18}N_2O_3$	206~209	63	67.11	6.34	9.78
							67.07	6.39	9.80
21	3,4-$(OMe)_2$	〃		$C_{14}H_{14}N_2O_3$	84~86	79	65.10	5.46	10.85
							65.16	5.41	10.87
22	〃	〃		〃	49~51	88	65.10	5.46	10.85
							65.08	5.43	10.88
23	〃	〃		$C_{15}H_{16}N_2O_3$	122~123	63	66.16	5.92	10.29
							66.12	5.97	10.24
24	〃	〃		〃	128~129	74	66.16	5.92	10.29
							66.19	5.88	10.33
25	〃	〃		〃	131~132	75	66.16	5.92	10.29
							66.20	5.96	10.25

26	3,4-(OMe)$_2$	H		$C_{16}H_{18}N_2O_3$	69~71	63	67.11 67.15	6.34 6.37	9.78 9.77
27	〃	〃	i-Pr	$C_{12}H_{17}NO_3$	144~145	85	64.55 64.59	7.68 7.61	6.27 6.23
28	〃	〃	n-Bu	$C_{13}H_{19}NO_3$	83~84	88	65.80 65.78	8.07 8.03	5.90 5.84
29	〃	〃	s-Bu	〃	127~128	83	65.80 65.84	8.07 8.04	5.90 5.93
30	〃	〃	i-Bu	〃	124~125	80	65.80 65.85	8.07 8.11	5.90 5.95
31	〃	〃		$C_{15}H_{21}NO_3$	181~182	91	68.41 68.36	8.04 8.07	5.32 5.36
32	3,5-(OMe)$_2$	〃		$C_{16}H_{18}N_2O_3$	96~97	85	66.16 66.12	5.92 5.98	10.29 10.32
33	〃	〃		$C_{16}H_{18}N_2O_3$	119~120	87	67.11 67.18	6.34 6.37	9.78 9.72
34	3,4,5-(OMe)$_3$	〃		$C_{18}H_{18}N_2O_4$	154~156	65	62.49 62.53	5.59 5.64	9.72 9.71
35	〃	〃		〃	157~158	77	62.49 62.52	5.59 5.56	9.72 9.73
36	〃	〃		$C_{18}H_{18}N_2O_4$	115~116	58	63.56 63.52	6.00 6.04	9.27 9.25
37	〃	〃		〃	145~146	69	63.56 63.51	6.00 6.07	9.27 9.22
38	〃	〃		〃	127~128	64	63.56 63.59	6.00 6.03	9.27 9.29

39	3,4,5-(OMe)$_3$	H		$C_{17}H_{20}N_2O_4$	145~146	71	64.54 64.58	6.37 6.32	8.86 8.90
40	〃	〃	n-Pr	$C_{12}H_{15}NO_4$	114~115	73	61.64 61.60	7.56 7.59	5.53 5.57
41	〃	〃	i-Pr	〃	154~155	77	61.64 61.66	7.56 7.54	5.53 5.58
42	〃	〃	n-Bu	$C_{14}H_{21}NO_4$	133~134	80	62.90 62.87	7.92 7.86	5.24 5.27
43	〃	〃	s-Bu	〃	162~163	75	62.90 62.95	7.92 7.94	5.24 5.20
44	〃	〃	t-Bu	〃	133~134	79	62.90 62.91	7.92 7.88	5.24 5.29
45	〃	〃	i-Bu	〃	122~123	81	62.90 62.96	7.92 7.87	5.24 5.28
46	〃	〃		$C_{16}H_{23}NO_4$	182~183	88	65.51 65.54	7.90 7.93	4.78 4.72
47	〃	i-Pr	i-Pr	$C_{16}H_{25}NO_4$	127~128	72	65.06 65.11	8.53 8.59	4.74 4.71

The compounds of this invention obtained in this way have excellent hypoglycemic action, and are effective at 100 mg/kg in man, and their effect is maintained by administration of 0.1-100 mg once a day for 24 hours or more.

For administration, a preparation is used which has been formed into the desired form by a customary means normally used in drug formulation.

Example 1

5-week-old mice (male, body weight 25-30g) with 5 animals in a group were fasted for 16 hours, and then alloxan at 75 mg/kg was administered intravenously. After 48 hours, a solution or suspension of a compound of this invention (200 mg/kg) was administered orally, and after 150 minutes, blood was taken from the heart and the glucose level was measured using glucose oxidase. The measurement results are exemplified in Table 2.

Table 2

Administered compound	Blood glucose value (mg/dl) mean ± S.D.
None (control)	473 ± 28
1	326 ± 42 **
3	378 ± 31 **
4	364 ± 19 ***
6	378 ± 52 *
7	412 ± 33 *
12	383 ± 28 **
17	345 ± 41 ***
22	378 ± 37 **
25	355 ± 46 **
26	336 ± 32 ***
27	407 ± 30 *
28	402 ± 24 **
29	421 ± 27 *
32	416 ± 23 *
33	402 ± 34 *
36	416 ± 21 **
38	307 ± 43 ***
39	412 ± 31 *
41	421 ± 28 *
46	383 ± 41 **

*: P < 0.05, **: P < 0.01, ***: P < 0.001

In the Table, the compound number corresponds to the compound number of the reference examples.

Example 2

4-methoxy-N-3-pyridylbenzamide (compound 1)	100 parts
calcium hydrogen phosphate	58.5 parts
crystalline cellulose	50 parts
corn starch	40 parts
calcium stearate	1.5 parts

These components were mixed well and pressed into 250 mg tablets (content of active component 100 mg/tablet) by usual methods, for use as a hypoglycemic agent.

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